Notice of Allowability	Application No. 08/905,293	Applicant(s) ROSOK ET AL.	
	Examiner S. Devi, Ph.D.	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *01/03/07*.

2. ☒ The allowed claim(s) ~~is~~/are *65-86, now renumbered as claims 1-22 respectively*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 01/04/07
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☒ Other *See Continuation Sheet*.

ATTACHMENT TO NOTICE OF ALLOWABILITY

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 01/03/07 in response to the non-final Office Action mailed 10/02/06. Applicants have amended the claims and the specification.

Examiner's Amendment

2) An Examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicants, an amendment may be filed as provided by 37 C.F.R 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee. The authorization to prepare this Examiner's amendment was provided by Mr. Todd Spalding in a telephonic interview on 16 March 2007.

This application has been amended as indicated below.

(a) Claims 1-7 and 11-63 have been canceled.

(b) New claims 65-86 have been added as indicated below.

--Claim 65 (New). A method of inhibiting IgG immunoglobulin-induced toxicity in a subject, said toxicity resulting from immunotherapy for a disease or *in vivo* diagnosis of a disease comprising administering to said subject an IgG immunoglobulin that binds to a target antigen associated with said disease, said IgG immunoglobulin having a variable region and a constant region comprising the CH_2 domain of said IgG, wherein said IgG is modified prior to the administration by structurally altering multiple toxicity-associated regions in the CH_2 domain of said constant region so that said administration inhibits said toxicity in said subject, wherein said multiple toxicity-associated regions are localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain, wherein the numbering of said amino acids is according to the 1991 Kabat amino acid numbering system.--

--Claim 66 (New). A method of inhibiting IgG immunoglobulin-induced toxicity in a subject, said toxicity resulting from immunotherapy for a disease or *in vivo* diagnosis of a disease comprising administering to said subject a structurally altered IgG antibody that binds to a target antigen associated with said disease, said structurally altered IgG antibody comprising a variable region and a constant region comprising the CH_2 domain of said IgG, wherein multiple toxicity-associated regions in the CH_2 domain of said constant region are modified prior to the administration so as to render said constant region unable to mediate an antibody dependent cellular cytotoxicity response or activate

complement, whereby said administration inhibits said toxicity in said subject, wherein said multiple toxicity-associated regions are localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain, wherein the numbering of said amino acids is according to the 1991 Kabat amino acid numbering system.--

--Claim 67 (New). A method of inhibiting IgG immunoglobulin-induced toxicity in a subject resulting from IgG fusion protein immunotherapy for a disease or *in vivo* diagnosis of a disease comprising administering to said subject an IgG fusion protein, wherein the IgG in the fusion protein binds to a target antigen specific to said disease and has a variable region and a constant region comprising the CH_2 domain, wherein said IgG in the fusion protein is modified prior to the administration by structurally altering multiple toxicity-associated regions in the CH_2 domain of said constant region so that said administration inhibits said toxicity in said subject, wherein said multiple toxicity-associated regions are localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain, wherein the numbering of said amino acids is according to the 1991 Kabat amino acid numbering system.--

--Claim 68 (New). A method for inhibiting IgG immunoglobulin-induced toxicity in a subject comprising:

(a) selecting an IgG which recognizes and binds to a target antigen, said target antigen being associated with a disease;

(b) mutating said IgG so selected by structurally altering multiple toxicity-associated regions in the CH_2 domain of the constant region of said IgG, thereby creating a structurally altered IgG having the modified CH_2 domain; and

(c) administering said structurally altered IgG of step (b) to said subject under conditions so that said structurally altered IgG recognizes and binds said target antigen,

wherein said multiple toxicity-associated regions are localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain wherein the numbering of said amino acids is according to the 1991 Kabat amino acid numbering system.--

--Claim 69 (New). A method for inhibiting IgG immunoglobulin-induced toxicity in a subject comprising:

(a) selecting an IgG fusion protein which recognizes and binds to a target antigen, said target antigen being associated with a disease;

(b) structurally altering multiple toxicity-associated regions in the CH_2 domain of the constant region of the IgG in said fusion protein so selected, thereby creating a structurally altered IgG fusion protein having the modified CH_2 domain; and

(c) administering said structurally altered IgG fusion protein of step (b) to said subject under conditions so that said structurally altered IgG fusion protein recognizes and binds said target antigen, wherein said multiple toxicity-associated regions are localized to amino acids 231-238 and amino acids 310-331 of the CH_2 domain wherein the numbering of said amino acids is according to the 1991 Kabat amino acid numbering system.--

--Claim 70 (New). The method of claim 66, wherein said antibody recognizes and binds Le^y.--

--Claim 71 (New). The method of claim 66, wherein said antibody recognizes and binds Le^x.--

--Claim 72 (New). The method of claim 65 or 68, wherein said immunoglobulin recognizes and binds Le^x.--

--Claim 73 (New). The method of claim 65 or 68, wherein said immunoglobulin recognizes and binds Le^y.--

--Claim 74 (New). The method of claim 66, wherein said antibody is monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.--

--Claim 75 (New). The method of claim 66, wherein said antibody is chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.--

--Claim 76 (New). The method of claim 65 or 68, wherein said immunoglobulin is monoclonal BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.--

--Claim 77 (New). The method of claim 65 or 68, wherein said immunoglobulin is chimeric ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.--

--Claim 78 (New). The method of claim 67 or 69, wherein said IgG fusion protein recognizes and binds Le^y.--

--Claim 79 (New). The method of claim 67 or 69, wherein said IgG fusion protein recognizes and binds Le^x.--

--Claim 80 (New). The method of claim 67 or 69, wherein said IgG fusion protein comprises the antigen binding site of monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.--

--Claim 81 (New). The method of claim 67 or 69, wherein said IgG fusion protein comprises the antigen binding site of chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.--

--Claim 82 (New). The method of claim 66, wherein said antibody is conjugated to a cytotoxic agent.--

--Claim 83 (New). The method of claim 65 or 68, wherein said immunoglobulin is conjugated to a cytotoxic agent.--

--Claim 84 (New). The method of claim 67 or 69, wherein said IgG fusion protein is conjugated to a cytotoxic agent.--

--Claim 85 (New). The method of claim 82, wherein the cytotoxic agent is selected from the group consisting of antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, and chemotherapeutic agents.--

--Claim 86 (New). The method of claim 65, 66, 67, 68 or 69 wherein said immunoglobulin-induced toxicity is gastrointestinal toxicity.--

Status of Claims

3) Claims 1-6, 53, 54-59 and 61-63 have been amended via the amendment filed 01/03/07.

Claims 8-10 and 64 have been canceled via the amendment filed 01/03/07.

Claims 1-6 and 11-63 have been canceled via this Examiner's amendment.

New claims 65-86 have been added via this Examiner's amendment.

Claims 65-86 are pending and are under examination.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' amendment information disclosure statement filed 01/04/07. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Replacement Drawings

5) Acknowledgment is made of Applicants' replacement formal drawings filed 01/03/07.

Objection(s) Withdrawn

6) The objection to the drawings made in paragraph 6 of the Office Action mailed 08/14/02 and

maintained in paragraph 7 of the Office Action mailed 06/02/04, paragraph 5 of the Office Action mailed 03/21/05 and paragraph 8 of the Office Action mailed 10/02/06 is withdrawn in light of Applicants' submission of replacement formal drawings.

Rejection(s) Moot

7) The rejection of claims 8-10 made in paragraph 16 of the Office Action 10/02/06 under 35 U.S.C § 112, first paragraph, as being non-enabled, is moot in light of Applicants' cancellation of the claims.

8) The rejection of claim 64 made in paragraph 17 of the Office Action 10/02/06 under 35 U.S.C § 112, first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claim.

9) The rejection of claims 8-10 and 64 made in paragraph 18 of the Office Action 10/02/06 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claims.

10) The rejection of claim 1 made in paragraph 13(b) and the rejection of claims 2-6 made in paragraph 13(c) of the Office Action mailed 06/02/04 and maintained in paragraph 18 of the Office Action mailed 03/21/05 and paragraph 15 of the Office Action 10/02/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

11) The rejection of claims 1-6, 11-22 and 28-31 made in paragraph 16 of the Office Action 10/02/06 under 35 U.S.C § 112, first paragraph, as being non-enabled, is moot in light of cancellation of the claims via this Examiner's amendment.

12) The rejection of claims 53-63 made in paragraph 17 of the Office Action 10/02/06 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is moot in light of Applicants' cancellation of the claims via this Examiner's amendment.

13) The rejection of claims 1-6, 11-22, 28-31 and 53-63 made in paragraph 18 of the Office Action 10/02/06 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claims via this Examiner's amendment.

14) The rejection of claims 1-6, 8-22, 28-31 and 53-64 made in paragraph 19 of the Office Action 10/02/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of the

cancellation of the claims by Applicants and via this Examiner's amendment.

15) The rejection of claims 1, 2, 5, 8, 28, 29, 53, 59 and 63 made in paragraph 21 of the Office Action 10/02/06 under 35 U.S.C § 102(a) as being anticipated by Slavin-Chiorini *et al.* (*Cancer Res.* 55: 5957s-5967s, 01 December 1995) as evidenced by Carlin *et al.* (*J. Nucl. Med.* 44: 1827-1838, 2003, abstract) and Cook *et al.* (*Cancer Biother. Radiopharm.* 11: 415-422, 1996, abstract), is moot in light of the cancellation of the claims by Applicants and via this Examiner's amendment.

16) The rejection of claims 1-6, 8, 11, 13-15, 17-19, 21, 22, 28-31, 53, 55-59 and 61-63 made in paragraph 22 of the Office Action 10/02/06 under 35 U.S.C § 102(e)(2) as being anticipated by Hellstrom *et al.* (US 6,020,145), is moot in light of the cancellation of the claims by Applicants and via this Examiner's amendment.

17) The rejection of claims 1, 5, 12, 16 and 20 made in paragraph 23 of the Office Action 10/02/06under 35 U.S.C. § 102(b) as being anticipated by Gundel *et al.* (WO 93/02702, already of record), is moot in light of the cancellation of the claims by Applicants and via this Examiner's amendment.

Remarks

18) Claims 65-86, now renumbered as claims 1-22 respectively, are allowed.

The descriptive support for the new claims is found in the canceled claims 1-6, 11-22, 28-31, 55-58 and 61-63; page 9-12; last full paragraph on page 13; pages 14-19 and 25; first two full paragraphs on page 23; last paragraph on page 24; paragraph bridging pages 30 and 31; and Examples 3-5.

19) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number (571) 273-8300, which receives facsimile transmissions 24 hours a day and 7 days a week.

20) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private

PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2007

S. DEVI, PH.D.
PRIMARY EXAMINER